IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Mohamed Attawia, Hassan Serhan, Thomas M. DiMauro, Melissa Grace and David Urbahns		
Application No.:	10/714,594	Group:	1649
Filed:	November 14, 2003	Examiner:	Hayes, Robert Clinton

Confirmation No.: 3230

For: Autologous Treatment of Degenerated Disc With Cells

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on

Date Signature

Typed or printed name of person signing certificate

APPEAL BRIEF

Mail Stop Appeal Brief Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Appeal Brief is submitted pursuant to the Notice of Appeal received in the U.S. Patent and Trademark Office on November 12, 2009, and in support of the appeal from the final rejections set forth in the Office Action mailed from the U.S. Patent and Trademark Office on May 12, 2009. The fee for filing a brief in support of an appeal is enclosed. A Petition for Extension of Time and the appropriate fee are being filed concurrently.

I. REAL PARTY IN INTEREST

The real party in interest is DePuy Spine, Inc., 325 Paramount Drive, Raynham Massachusetts 02767-0350. DePuy Spine, Inc. is the Assignee of the entire right, title and interest in the subject application by virtue of an Assignment recorded on April 2, 2004 at Reel 015160, Frames 0454-0458.

II. RELATED APPEALS AND INTERFERENCES

Appellants, the undersigned Attorney and Assignee are not aware of any related appeals, interferences or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1-4, 6, 7, 11-17, 20-24 and 31-34 have been finally rejected, and a copy of these claims appears in the Claims Appendix of this Brief. Claims 1, 6, 7, 11-17, 20-24, 32 and 33 were amended. Claims 2-4 and 31 appear as originally filed. Claims 5, 8-10, 18, 19 and 25-30 were canceled. Claim 34 was added in the Amendment filed on October 31, 2007. Claims 1-4, 6, 7, 11-17, 20-24 and 31-34 are being appealed herein.

IV. STATUS OF AMENDMENTS

No amendments have been filed subsequent to the final rejections in the Office Action mailed from the U.S. Patent and Trademark Office on May 12, 2009.

V. SUMMARY OF CLAIMED SUBJECT MATTER

In one embodiment as set forth in the independent Claim 1, the subject matter pertains to a method of treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc. (Specification, for example, at page 6, lines 8-11).

In another embodiment as set forth in the independent Claim 32, the subject matter pertains to a method of treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering a growth factor in the TGF-β superfamily and autologous uncultured mesenchymal stem cells embedded in collagen gel into a degenerated intervertebral disc in a formulation with a volume of between more than 0.5 mL and about 3.0 mL. (Specification, for example, at page 6, lines 8-11; page 10, lines 5-29; and page 13, lines 7-10).

In another embodiment as set forth in the independent Claim 33, the subject matter pertains to a method of treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc immediately following harvesting of the autologous uncultured

mesenchymal stem cells in a formulation with a volume of between more than 0.5 mL and about 3.0 mL. (Specification, for example, at page 4, line 26 to page 5, line 5; and page 13, lines 7-10).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection presented for review are:

A. Whether Claims 1-3, 6, 11-16, 20-24, 31 and 33 are properly rejected under 35 U.S.C. § 103(a) over Sakai *et al.* (Sakai *et al.*, "Transplantation of Mesenchymal Stem Cells Embedded in Atelocollagen® Gel to the Intervertebral Disc: A Potential Therapeutic Model for Disc Degeneration," *Biomaterials*, 24: 3531-3541(2003); hereinafter, "Sakai *et al.*").

B. Whether Claims 1-3, 6, 7, 11-16, 20-24, 31 and 33 are properly rejected under 35 U.S.C. § 103(a) over Sakai *et al.* and further in view of El-Khoury *et al.* (El-Khoury, G. *et al.*, "Percutaneous Procedures for the Diagnosis and Treatment of Lower Back Pain: Diskography, Facet-Joint Injection, and Epidural Injection," *Am. J. Roentgenol.*, 157(4): 685-691 (1991); hereinafter, "El-Khoury *et al.*").

C. Whether Claims 1-3, 6, 11-14, 15, 16, 20-24, 31, 33 and 34 are properly rejected under 35 U.S.C. § 103(a) over Sakai *et al.* and further in view of McMillan *et al.* (McMillan, D. *et al.*, "Intra-Operative Autologous Blood Management," *Transfusion and Apheresis Science*, 27(1): 73-81 (2002); hereinafter, "McMillan *et al.*").

D. Whether Claims 1-4, 6, 11-16, 20-24, 31 and 33 are properly rejected under 35 U.S.C. § 103(a) over Sakai *et al.* and further in view of Tanny *et al.* (Tanny, G.B. *et al.*, "Improved Filtration Technique for Concentrating and Harvesting Bacteria," *Appl. Environ. Microbiol., 40*(2):269-273 (1980); hereinafter, "Tanny *et al.*").

E. Whether Claims 1-3, 6-7, 11-16, 20-24, 31-33 are properly rejected under 35 U.S.C. §103(a) over Sakai *et al.* and further in view of Russell *et al.* "Human Bone Marrow Mesenchymal Stromal Cells as a Source of Chondrocytes for Treatment of Intervertebral Disc Degeneration," 27, Abstracts of the 30th Annual Meeting of the

International Society for the Study of the Lumbar Spine, Vancouver, Canada (May 2003); hereinafter, "Russell *et al.*").

F. Whether Claims 1-3, 6, 7, 11-16, 20-24 and 31-33 are properly rejected under 35 U.S.C. § 103(a) over Sakai *et al.* and in view of Russell *et al.* and further in view of El-Khoury *et al.*

VII. ARGUMENTS

Introduction

The primary reference in each rejection, Sakai *et al.*, teaches administration of cultured mesenchymal cells (MSCs) into the spinal discs of rabbits. In contrast, the appealed claims are directed to the use of uncultured MSCs to treat degenerative disc disease.

The common knowledge in the art at the time of the invention, and factual as well as declaratory evidence submitted before the Office, unequivocally show that administering uncultured autologous MSCs into the disc was contrary to widely accepted wisdom in the art at the time of the invention and would not be expected to yield predictable results with a reasonable expectation of success. One of ordinary skill in the art would not have been motivated to combine or modify the teachings of the prior art to arrive at the claimed invention. Therefore, a *prima facie* case of obviousness has not been established.

A. *Claims 1-3, 6, 11-16, 20-24, 31 and 33 are patentable under 35 U.S.C. § 103(a) over Sakai et al.*

In *KSR v. Teleflex*, 550 U.S. 393 (2007), the United States Supreme Court reaffirmed the framework for determining obviousness under 35 U.S.C. § 103 established in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). The Court in *Graham* stated that explicit findings should be made with respect to: (1) the scope and content of the prior art; (2) difference between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) secondary considerations, such as unexpected results. The legal question of obviousness should then be assessed against this factual background.

With regard to the scope and content of the prior art, the cited reference, Sakai *et al.*, discloses the use of cultured MSCs for the treatment of intervertebral disc degeneration in rabbits. Sakai *et al.* teach that the MSCs are found in small numbers (Sakai *et al.*, page 3532, left column, 4th full paragraph). Due to this limited availability of MSCs, Sakai *et al.* teach culturing and expansion of the MSCs and explore potential therapeutic models using Atelocollagen® gel which allows expansion of the MSCs while loading them onto the gel matrix. Specifically, the cultured cells were embedded in the Atelocollagen® and the solution was transplanted in the spinal discs of rabbits. Sakai *et al.* specifically recite that: "In order to use in cell cultures, Atelocollagen® solution was neutralized..." *Id.* at page 3538, left col., first paragraph; emphasis added. Thus, cell culturing was employed to expand the MSCs while loading the cells onto the Atelocollagen® matrix.

With regard to the differences between Sakai *et al.* and the claims at issue, unlike the pending claims, Sakai *et al.* do not teach or suggest administering *uncultured* MSCs. The level of ordinary skill in the art at the time of the invention was the level of skill possessed by a Ph.D. or M.D. level scientist in the field of regenerative medicine in an academic or clinical setting.

The Examiner acknowledged that Sakai *et al.* do not teach administration of uncultured MSCs to treat a degenerative intervertebral disc (*see* the Office Action at page 3, third paragraph). The Examiner's rejection is based on the rationale that the missing element (*i.e.*, using uncultured MSCs) is an equivalent or obvious variant to the widely known, practiced method of culturing MSCs. The Examiner's position is that one of ordinary skill in the art could simply do away with the culturing of the MSCs and implant uncultured MSCs into the disc. However, the prior art, the general knowledge available in the art, and common sense in the art at the time of the invention all contradict the assumption that the use of uncultured MSCs is an equivalent or obvious variant leading to predictable results. The general knowledge available in the art at the time of the invention strongly supports Sakai *et al.*'s approach. It was widely known that MSCs available in the bone marrow were extremely scarce and limited, and it was conventional to expand MSCs by cell culture before therapeutic use. Appellants demonstrate this fact with evidentiary submissions, which were improperly dismissed.

The Examiner dismissed relevant evidence establishing non-obviousness and unpredictability of administering uncultured MSCs

I. Declaration of Dr. Attawia

To indicate the state of the art at the time of the invention, Appellants submitted a Declaration by one of the inventors, Dr. Mohamed Attawia, on June 27, 2008 (hereinafter, the "Declaration"). Dr. Attawia, a researcher and physician for twenty years and a person having at least ordinary skill in the art in the field of tissue engineering and bone repair involving spinal disc injuries, unequivocally stated that one of ordinary skill in the art heavily relied on cultured MSCs for cell-based therapy at the time of the invention. In the Declaration, Dr. Attawia stated that the use of uncultured MSCs to treat degenerative disc disease was not an obvious option to one of ordinary skill in the art. Specifically, Dr. Attawia stated that: (1) because at the time of the invention, it was general knowledge that MSCs are pluripotent cells found in the body in extremely small numbers, persons believed that expansion of the cells by culturing was necessary before transplantation (*see* the Declaration, paragraphs 7-8); (2) Sakai *et al.* teach administering cultured cells from the outset because Sakai *et al.*'s mode of cell delivery requires cell culture expansion (*see* the Declaration, paragraphs 12-14); (3) Caplan and Haynesworth (which were also cited by Sakai *et al.*) also taught methods of cell culture expansion at the time of the invention (*see* the Declaration, paragraphs 15-17); (4) it was common consensus in the field that cell culture expansion was required for the effective administration of MSCs for treatment (*see* the Declaration, paragraph 15); and (5) the state of the art evidenced by Centeno *et al.*, was to rely on the culturing of MSCs to prepare for implantation (*see* the Declaration, paragraph 18).

In spite of Dr. Attawia's detailed and well-informed statements, the Office Action disregarded the Declaration, stating:

> ...although Declarant is correct that Sakai et al. does not teach use of uncultured MSC (cells) to treat a degenerative intervertebral disc, different motivations (e.g., as actually made by the Examiner in the pending rejections) are not required to be the same as those presented, or putatively presented, by Sakai: especially when Declarant's opinion on what Sakai et al may have also thought, or not, is not supportable. (the Office Action at page 3, third paragraph; emphasis added)

Dismissing such declaratory evidence in favor of the Examiner's motivation is largely at odds with current patent law and rules (*see* the Manual of Patent Examining Procedure (MPEP)

§716.01(a)) citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, U.S.P.Q. 871, 879 (Fed. Cir. 1983). The MPEP § 716.01(c)(III) also states that: "[opinion] testimony is entitled to consideration and some weight so long as the opinion is not on the ultimate legal conclusion at issue." Declaratory evidence ("opinion testimony"), such as the Declaration by Dr. Attawia, should be entitled to substantial consideration, especially when such opinion is supported by the factual statements in the references, namely Sakai *et al.* and Centeno *et al.*

II. Centeno *et al.*

Centeno *et al.* (Centeno *et al.*, *Pain Physician*, 11(3): 343-353 (2008); hereinafter, "Centeno *et al.*"; previously submitted as "Exhibit A" to the Declaration by Dr. Attawia filed with the U.S. Patent and Trademark Office on June 27, 2008) disclose that the number of MSCs which can be isolated from bone marrow is extremely scarce (*e.g.*, "1 out of 10,000-1,000,000" bone marrow nucleated cells) and state that: "most research in cartilage regeneration has focused on the use of culture expanded cells." page 345, right col., 1st-2nd paragraphs. Centeno *et al.* establish that even at the time when Centeno *et al.* was published (2008), five years following the filing of the present application, one of ordinary skill in the art continued to rely on culturing and expansion of MSCs.

The Examiner disregarded this evidence, stating that: "…Declarant's reliance on a reference published 5 years after the priority of the instant application as basis to what he thinks should have been obvious to 'scientists of ordinary skill in the art of regenerative medicine' is also not persuasive, because obviousness is determined as of the filing date of the instant application" (Office Action at page 4, first paragraph).

This dismissal of Centeno *et al.* as an irrelevant post-filing reference is clear error because objective documentary evidence relevant to the issue of the state of the art at the time of the invention must be considered by the Examiner even if post-filing. The MPEP expressly allows post-filing evidence to be considered by the Examiner in a number of circumstances, for example:

> Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. *In re Hogan*, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the

> disclosed invention was not possible at the time of filing and should be considered. MPEP § 2164.05(a).

Significantly, the MPEP also states:

> References which do not qualify as prior art because they postdate the claimed invention may be relied upon to show the level of ordinary skill in the art at or around the time the invention was made. MPEP § 2141.03 citing *Ex parte Erlich*, 22 USPQ 1463 (Bd. Pat. App. & Inter. 1992).

Centeno *et al.* unequivocally indicate the state of the art regarding MSC-based therapy for cartilage regeneration at the time of the invention and what one of ordinary skill in the art at the time of the invention would have known on or before the effective filing date of the patent application:

> Since it is MSCs that are capable of differentiating into cartilage, their use as cellular building blocks that can be implanted via fluoroscopically guided percutaneous procedures has some face validity. As discussed above, the number of MSCs that can be isolated from bone marrow is fairly limited. As a result, most research in cartilage regeneration has focused on the use of culture expanded cells. This means that cells are isolated and then placed into various growth factors to be grown to higher numbers over a period of weeks in an *ex-vivo* monolayer culture (Centeno *et al.*, at page 345, right col., second paragraph; emphasis added; citation omitted)

For the statements emphasized above, Centeno *et al.* (2008) cited four references whose publication dates range from the year that the present application was filed (2003) to 2007. Therefore, although the Centeno *et al.* reference is a post-filing reference, it provides factual evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. *See In re Hogan*, 559 F.2d at 595 at 605. Therefore, contrary to the statement in the Office Action, the Centeno *et al.* reference strongly supports finding that one of ordinary skill in the art would not have administered uncultured MSCs based on the knowledge available at the time of the invention.

III. Caplan *et al.* and Haynesworth *et al.*

As discussed above, with respect to the state of the art at the time of the invention, Dr. Attawia discussed the works of Caplan and Haynesworth who, like Sakai *et al.*, taught various MSC expansion methods prior to implantation. Caplan's work is cited by Sakai *et al.* as well as by Centeno *et al.* for teachings directed to MSC expansion by culture. In response, the Examiner stated that: "Nor are any teachings of Caplan *et al.* or Haynesworth *et al.* part of the instant rejection" (Office Action at page 4; first paragraph) and dismissed this declaratory evidence by Dr. Attawia. This dismissal is incorrect because these teachings do not support the rejection. Rather, the references demonstrate that the rejection is improper: the citations by Sakai *et al.* and Centeno *et al.* establish that Dr. Attawia's statements regarding Caplan and Haynesworth are highly relevant to the state of the art and what one of ordinary skill in the art believed at the time of the invention regarding the importance of cell culture expansion.

The Rejection was not supported by objective evidence

As noted above, Sakai *et al.* teach culturing of the MSCs based on widely accepted knowledge at the time of the invention. A motivation for expanding MSCs was revealed in Sakai *et al.*, as well as in general knowledge available to one of ordinary skill in the art at the time of the invention, as indicated by Centeno *et al.* and supported by the declaratory evidence of Dr. Attawia. In contrast, no evidence has been proffered to support the assumption that there was no requirement for culturing MSCs, or that not culturing was believed to be a simple substitution for culturing which would lead to predictable results (for example, see Office Action at page 5, second paragraph). To rely on common knowledge or take on Official Notice, facts must be capable of instant and unquestionable demonstration as well-known; and assessment of basic knowledge and common sense must be based on evidence in the record. "It is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record, as the principal evidence upon which a rejection was based" (MPEP § 2144.03 (A) citing *In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001)).

Further, contrary to the statements in the Office Action, administration of uncultured MSCs, particularly into the disc, was not known to be suitable for the intended use of the claimed invention (*i.e.*, treatment of degenerative disc disease) at the time of the invention. The Office Action stated that: "the motivation to combine or substitute can arise from the expectation that the prior art elements (*i.e.*, cultured or uncultured MSCs) will perform their expected

functions to achieve their expected results (*i.e.*, treat degenerative disc disease) when combined or substituted for their common known purpose" (Office Action at page 6, first paragraph, last sentence). In an attempt to support this assertion, the Examiner cited MPEP § 2144.07. ("Art Recognized Suitability for an Intended Purpose"). To apply MPEP § 2144.07, however, the element at issue must be a *known method* based on its *suitability for its intended use*. The issue is whether one of ordinary skill in the art would recognize that *uncultured MSCs* would be suitable for an intended use to treat a degenerative disc disease. Here, administering uncultured MSCs, particularly into the disc to treat a degenerative disc disease, was not known to be suitable for the intended purpose at the time of the invention. In fact, the suitability for using uncultured cells (*i.e.*, MSCs) to treat degenerative disc disease was not established before the present invention, which resulted from proceeding contrary to accepted wisdom in the art. Courts have stated that proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

The rejection is based on impermissible hindsight

Despite the teachings in Sakai *et al.* and the statements by Centeno *et al.* and Dr. Attawia regarding the state of the art, the Office Action stated: "...different motivations (*e.g., as actually made by the Examiner in the pending rejections*) are not required to be the same as those presented, or putatively presented, by Sakai" (the Office Action at page 3, first paragraph; emphasis added). The Office Action went on to state that any assertion of what Sakai's intentions were is "mere speculation" and that: "*The Examiner's position remains that no requirement for culturing reasonably existed based on a fair reading of Sakai et al.*, nor does Sakai reasonably 'teach away' from Applicant's claimed invention, in contrast to Applicants'/Declarant's assertions" (Office Action at page 5, second paragraph; emphasis added).

This analysis indicates that the rejection is based on improper hindsight, a subjective belief or motivation, and a disregard of objective factual evidence presented before the Office. The motivation to modify the teachings of prior art to arrive at an invention must be determined based on the knowledge available to one of ordinary skill in the art at the time the invention was made. According to MPEP § 2141.01(III), the requirement that obviousness is determined at the time of the invention was made "is to avoid impermissible hindsight."

Here, the rejection was improperly based on the Examiner's present subjective belief and motivation without no evidentiary support. Moreover, the objective factual evidence presented before the Office (*i.e.*, (1) the declaratory evidence of Dr. Attawia, (2) the teachings in the cited prior art reference, Sakai *et al.*, and (3) the statements of submitted references evidencing the state of the art at the time of the invention, *e.g.*, Centeno *et al.*) was disregarded.

Further, the claimed invention is in the biotechnology and chemical arts in an unpredictable field. The *KSR* court clarified that predictability is a factor relevant to obviousness. *KSR*, 550 U.S. at 421. The Federal Circuit in *Abbott Laboratories v. Sandoz, Inc.*, 544 F.3d 1341, 1351, stated that:

> We agree that the obviousness of selection of components, when there is no prediction in the prior art as to the results obtainable from a selected component, differs from the issue in *KSR*, where the Court provided guidance that "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." citation omitted; emphasis added.

At the time of the invention, administering uncultured cells was not predictable. Because the widely accepted conventional knowledge at the time of the invention was that only a small number of MSCs can be isolated from the bone marrow and that the MSCs can be easily cultured, one of ordinary skill in the art would have tried obvious approaches, for example, to refine and improve the culturing step (*e.g.*, minimizing contamination levels or maximizing cell growth or homogeneity); or to incorporate the cell expansion step into the preparation of a therapeutic formulation step (*e.g.*, *see* Sakai *et al.* in which MSCs were cultured and loaded in the Atelocollagen® gel). As established by the evidence discussed above, one of ordinary skill in the art would not have been motivated to use uncultured MSCs because doing so was not a widely accepted, identified, or predictable solution available at the time of the invention, particularly for treating degenerative disc disease. Further, because of the limited availability of the MSCs, one of ordinary skill in the art would not have been motivated to modify Sakai *et al.* with a reasonable expectation of success in arriving at the present invention.

In summary, common knowledge in the art at the time of the invention and objective factual as well as declaratory evidence submitted before the Office unequivocally establish that administering uncultured autologous MSCs into the disc was contrary to widely accepted

wisdom in the art at the time of the invention. Accordingly, the teachings of Sakai *et al.* do not render Claims 1-3, 6, 7, 11-16, 20-24, 31 and 33 obvious.

B. Claims 1-3, 6, 7, 11-16, 20-24, 31 and 33 are patentable under 35 U.S.C. § 103(a) over Sakai et al. and in view of El-Khoury et al.

As discussed above, the Examiner concedes that Sakai *et al.* do not teach the use of uncultured MSCs, and the objective evidence submitted by Appellants establishes that one of skill in the art would not have been motivated to administer uncultured MSCs in the invention with a reasonable expectation of success.

In this rejection, the Examiner has cited El-Khoury *et al.* on the grounds that it teaches administration of an agent to an intervertebral disc at a total volume of 2.5 ml for the treatment of back pain (El-Khoury *et al.*, pages 686 and 688). El-Khoury *et al.* do not teach or suggest any aspect relating to directly administering uncultured autologous MSCs.

The teachings of El-Khoury *et al.* simply do not compensate for the deficiencies in Sakai *et al.* with regard to the claimed novel use of uncultured cells. Accordingly, the combined teachings of Sakai *et al.* and El-Khoury *et al.* do not render Claims 1-3, 6, 7, 11-16, 20-24, 31 and 33 obvious.

C. Claims 1-3, 6, 11-14, 15, 16, 20-24, 31, 33 and 34 are patentable under 35 U.S.C. § 103(a) over Sakai et al. and in view of McMillan et al.

The Office Action states that:

> Consistent with that held by the Supreme Court in KSR International Co. v. Teleflex Inc. et al. (82 USPQ2d 1385 (2007)), in which the simple substitution of one known, equivalent element [i.e., an intraoperative procedure to transplant/transfuse autologous RBCs] for another to obtain predictable results [i.e., intraoperative procedure to transplant autologous MSCs], or the combining of prior art elements [i.e., culturing versus nonculturing cells] according to known methods [of eventually proliferating the same MSCs cells *in vivo* in a transplanted matrix] to yield predictable results [i.e., treatment of the degenerative disc disease], reasonably supports a *prima facie* case of obviousness, especially given a finite number of predictable solutions [i.e., culturing or not culturing MSCs cells before addition of matrix gel for subsequent implantation, and use of uncultured autologous MSCs] where it

> would be obvious to try based on the state of the art at the time of filing Applications' invention (i.e., 2003). (Office Action at page 8, second paragraph).

The deficiencies of Sakai *et al.* with regard to administering uncultured autologous MSCs as well as common knowledge available in the art at the time of the invention as supported by objective evidence is discussed in detail above.

McMillan *et al.* teach intraoperative transfusion of autologous blood cells in which the autologous blood cells are re-transfused into a patient after being harvested from the same patient. As noted above, Sakai *et al.* and other objective evidence support the fact that MSCs are unique in that they are found in very small numbers. In contrast, the red blood cells are available in abundance. While the red blood cells were known to be available in abundance for intraoperative procedures, the MSCs were known to be available in limited numbers. Based on the common knowledge available in the art at the time of the invention, the predictability of a successful therapeutic outcome with uncultured MSC-based cell therapy was extremely low as compared to that of transfusing uncultured red blood cells.

One of ordinary skill in the art would have clearly recognized the differences involved in preparing red blood cells and MSCs for implantation because the technical problems imposed on those handling MSCs are not equivalent to those imposed on those handling red blood cells. One of ordinary skill in the art would have clearly understood that the techniques conventionally employed in preparing blood cells for transfusion would not have applied to MSCs due to the uniqueness of the MSCs, and would not have been motivated to combine the teachings of Sakai *et al.* with the teachings of McMillan *et al.* with a reasonable expectation of success. Further, the use of uncultured MSCs was not a predictable solution or option which would lead to predictable results. See *Abbott Laboratories*, 544 F.3d at 1351. Therefore, the combined teachings of Sakai *et al.* and McMillan *et al.* do not render Claims 1-3, 6, 11-14, 15, 16, 20-24, 31, 33 and 34 obvious.

D. Claims 1-4, 6, 11-16, 20-24, 31 and 33 are patentable under 35 U.S.C. § 103(a) over Sakai et al. and in view of Tanny et al.

The deficiencies of Sakai *et al.* are discussed in detail above. To support the rejection, the Examiner reiterated his position regarding predictability. However, as established by the

objective evidence and the teachings of the cited references, the present invention employing uncultured MSCs was not a predictable option which would lead to predictable results. Tanny *et al.* merely teach a method of concentrating bacterial cells by filtration and harvesting them by culture. Similar to Sakai *et al.*, the bacterial cells taught in Tanny *et al.* were *cultured.* Furthermore, similar to the red blood cells taught by McMillan *et al.*, the bacterial cells in Tanny *et al.* have widely different properties from the MSCs of the present invention. One of ordinary skill in the art would have clearly understood that the technique described by Tanny *et al.* could not have been applied to the present invention involving uncultured autologous MSCs with a reasonable expectation of success. Simply, Tanny *et al.*, do not compensate for the deficiencies in Sakai *et al.* Therefore, the combined teachings of Sakai *et al.* and Tanny *et al.* do not render Claims 1-4, 6, 11-16, 20-24, 31 and 33 obvious.

E. Claims 1-3, 6-7, 11-16, 20-24 and 31-33 are patentable under 35 U.S.C. § 103(a) over Sakai et al. and in view of Russell et al.

The deficiencies of Sakai *et al.* are discussed in detail above. Russell *et al.* teach the use of human bone marrow mesenchymal stromal cells as a source of chondrocytes for the treatment of intervertebral disc degeneration. Russell *et al.* teach that the cells were cultured in the presence of the growth factor, TGF-β1, to promote expansion of MSCs. Russell *et al.* reinforce Appellants' position that that one of ordinary skill in the art would have cultured MSCs at the time of the invention. In fact, Russell *et al.* even suggested adding "growth factor such as TGF-B1 in order to increase the rate of growth for the cultured cells." One of ordinary skill in the art would not have been motivated to combine the teachings of Sakai *et al.* with Russell *et al.* to arrive at Appellants' invention with a reasonable expectation of success. Therefore, the combined teachings of Sakai *et al.* and Russell *et al.* do not render Claims 1-3, 6-7, 11-16, 20-24 and 31-33 obvious.

F. Claims 1-3, 6, 7, 11-16, 20-24 and 31-33 are patentable under 35 U.S.C. § 103(a) over Sakai et al. in view of Russell et al. and further in view of El-Khoury et al.

The deficiencies of Sakai *et al.* are discussed in detail above. Russell *et al.* teach culturing and expanding isolated MSCs using a growth factor such as TGF-β1. El-Khoury *et al.* teach administration of an agent into the disc at a particular volume of 2.5 ml. As discussed in

detail above, the teachings of Sakai *et al.* and Russell *et al.* strongly support Appellants' position that one of ordinary skill in the art would have cultured MSCs. Further, El-Khoury *et al.* fails to compensate the deficiencies in Sakai *et al.* and Russell *et al.* Based on teachings of the combined references and general knowledge available in the art, one of ordinary skill in the art would not have been motivated to modify the teachings of Sakai *et al.*, Russell *et al.*, and El-Khoury *et al.* to arrive at the present invention (*i.e.*, the use the uncultured MSCs to treat degenerative disc disease). Therefore, the combined teachings of Sakai *et al.*, Russell *et al.* and El-Khoury *et al.* do not render Claims 1-3, 6, 7, 11-16, 20-24 and 31-33 obvious.

In view of the foregoing, Appellants respectfully request that the final rejection of Claims 1-4, 6, 7, 11-17, 20-24 and 31-34 be reversed with a recommendation that the application be passed to issue.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Deirdre E. Sanders

Deirdre E. Sanders
Registration No.: 42,122
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

Dated: May 12, 2010

CLAIMS APPENDIX

1. A method of treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc.

2. The method of Claim 1, wherein the cells are concentrated prior to being administered into the intervertebral disc.

3. The method of Claim 2, wherein the cells are concentrated by centrifugation.

4. The method of Claim 2, wherein the cells are concentrated by filtration.

6. The method of Claim 1, wherein the cells are administered to the disc using a carrier, wherein the carrier is selected from the group consisting of beads, microspheres, nanospheres, hydrogels, gels, polymers, ceramics, collagen and platelet gels.

7. The method of Claim 1, wherein an additional therapeutic agent is administered into the intervertebral disc, and wherein said additional therapeutic agent is TGF-β.

11. The method of Claim 7, wherein the TGF-β and the cells are administered into the intervertebral disc using a carrier, wherein the carrier is selected from the group consisting of beads, microspheres, nanospheres, hydrogels, gels, polymers, ceramics, collagen and platelet gels.

12. The method of Claim 7, wherein the TGF-β is administered simultaneously with administering the cells to the disc.

13. The method of Claim 7, wherein the TGF-β is administered prior to administering the cells to the disc.

14. The method of Claim 7, wherein the TGF-β is administered after administering the cells to the disc.

15. The method of Claim 1, wherein the cells are administered into the intervertebral disc in a formulation with a volume of between more than 0.5 ml and about 3.0 ml.

16. The method of Claim 15, wherein the carrier comprises a hydrogel.

17. The method of Claim 15, wherein the carrier comprises microspheres.

20. The method of Claim 15, wherein the cells are administered into the nucleus pulposus of the disc.

21. The method of Claim 15, wherein the cells are administered into the annulus fibrosus of the disc.

22. The method of Claim 15, wherein a portion of the nucleus pulposus is removed prior to administering the cells into the intervertebral disc.

23. The method of Claim 15, wherein the cells are administered through a needle.

24. The method of Claim 23, wherein the needle bore has a maximum gauge of about 24 gauge.

31. The method of Claim 1, wherein the formulation is administered in an amount of less than about 1 ml.

32. A method of treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering a growth factor in the TGF-β superfamily and autologous uncultured mesenchymal stem cells embedded in collagen gel into a degenerated intervertebral disc in a formulation with a volume of between more than 0.5 mL and about 3.0 mL.

33. A method of treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc immediately following harvesting of the autologous uncultured mesenchymal stem cells in a formulation with a volume of between more than 0.5 mL and about 3.0 mL.

34. The method of Claim 1, wherein the cells are provided intra-operatively to a patient following harvest from the patient.

EVIDENCE APPENDIX

1. The Declaration Under 37 C.F.R. § 1.132 by Mohamed Attawia M.D. filed on June 27, 2008.

2. A copy of Centeno *et al.* previously submitted as Exhibit A with the Declaration Under 37 C.F.R. § 1.132 by Mohamed Attawia M.D., filed on June 27, 2008 (Centeno *et al.*, "Increased Knee Cartilage Volume in Degenerative Joint Disease Using Percutaneously Implanted, Autologous Mesenchymal Stem Cells" *Pain Physician* 11:343-353 (2008)).

RELATED PROCEEDINGS APPENDIX

None